Under-recognised macrophage activation syndrome in multisystem inflammatory syndrome in children

Sirs,

Multisystem inflammatory syndrome in children (MIS-C) is a serious paediatric disease associated with coronavirus disease 2019 (COVID-19) (1-3). It is characterised by hyperinflammation and multi-organ dysfunction in patients with a history of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection (2). Many patients with MIS-C present with 'Kawasaki disease (KD)-like features' including rash, conjunctivitis, or mucocutaneous lesions (3). The presence of KD-like features in patients with MIS-C has received clinical attention, but the extent of organ dysfunction in patients with MIS-C is of greater importance as it directly affects the disease course and outcome (4, 5)

Organ dysfunction is also seen in macrophage activation syndrome (MAS), which is a life-threatening complication of various paediatric inflammatory diseases (6-9). MAS, which is part of the spectrum of secondary haemophagocytic lymphohistiocytosis (HLH), is caused by excessive activation of T cells and macrophages (6). This uncontrolled immune response causes persistent fever, splenomegaly, cytopenia, and hyperferritinemia, which are the key features of MAS (7, 8). MAS usually develops from exacerbation of a primary disease, such as systemic juvenile idiopathic arthritis (sJIA), systemic lupus erythematosus (SLE), or KD (7). Recently, it has been reported that MIS-C can be complicated with MAS (8). Early recognition of MIS-C and/or MAS is essential but sometimes challenging due to similar clinical and laboratory findings in various paediatric inflammatory diseases (6, 9). Here, we present an atypical case of MIS-C complicated with MAS and discuss the relationship between MIS-C and MAS.

A 14-year-old boy was referred from a general hospital due to a five-day history of fever, abdominal pain, and headache. The patient had been diagnosed with COVID-19 through a polymerase chain reaction (PCR) test four weeks prior to his presentation. On admission, physical and neurological examinations were unremarkable except for abdominal tenderness. Blood tests showed an elevated C-reactive protein (CRP). Abdominal computed tomography (CT) ruled out appendicitis, but showed wall oedema in the small intestine and splenomegaly. The patient was given empiric antibiotics (ceftriaxone) for three days. However, his fever and headache persisted, and neck stiffness was evident on neurological examination. Cerebrospinal fluid (CSF) examination showed normal protein and glucose levels but an increased leukocyte count (270/μL). Considering the possibility of bacterial meningitis, vancomycin was added. The meningitis panel PCR for major pathogens and CSF culture were negative. However, blood tests revealed hyperinflammation and multi-organ dysfunction characterised by leukopenia and thrombocytopenia, worsening CRP and ferritin levels, elevated cardiac and liver enzymes, and coagulopathy. At that point, we realised that his clinical manifestations met both the MIS-C definition and the MAS criteria (Table I).

KD complicated with MAS is diagnosed when KD patients present with systemic inflammation severe enough to meet ≥5/8 criteria for MAS (Fig. 1A-B). Infectious triggers (*e.g.* Epstein Barr virus, influenza virus, or group A *Streptococcus*) and organ dysfunction (*e.g.* shock, neurologic, or renal) may be found in KD but are not included in the diagnostic criteria for KD and/or MAS (4, 7). Similarly, 'MIS-C complicated with MAS' is diagnosed when severe systemic inflammation (*i.e.* ≥5/8 criteria for MAS) is identified in a patient with SARS-CoV-2 infection and organ dysfunction (Fig. 1C-D). KD-like features in patients with MIS-C are an interesting finding but are not essential in diagnosing MIS-C and/or MAS (2, 10).

As seen in our patient, the absence of KD-like features may delay the diagnosis of MIS-C or MIS-C complicated with MAS. It has been reported that a significant proportion (25-50%) of MIS-C patients do not exhibit KD-like features in the early stages of their disease, and nearly one-third of MIS-C patients do not exhibit KD-like features throughout their disease (5). More importantly, the clinical course of MIS-C without KD-like features is usually more severe than that of MIS-C with KD-like features (with regard to complications, intensive care unit admission, or mortality) (11). Therefore, it is necessary to consider the possibility of under-recognised MIS-C and/or MAS in patients with unexplained systemic inflammation or organ dysfunction, even in the absence of KD-like features (4, 9).

It is clinically interesting that the same variables are used to diagnose MIS-C and MAS

Table I. MIS-C definition, MAS criteria, and clinical and laboratory findings of our patient.

MIS-C (CDC and RCPCH definition) (1, 3)	MAS (HLH-2004 criteria) (6, 7)	14-year-old boy in this study
I. Systemic inflammation	The diagnosis of MAS is met if ≥ 5 of 8 criteria are present:	I. Systemic inflammation
Fever > 38.0°C in a patient aged < 21 years	1. Fever	Persistent fever
Hepatosplenomegaly on ultrasonography	2. Splenomegaly	Splenomegaly on abdominal CT
Lymphopenia or thrombocytopenia	3. Cytopenia ≥ 2 cell lines	Leukocytes, 3630/μL; platelets, 98000/μL
Elevated CRP (≥ 3.0 mg/dL), PCT, AST, ALT, or LDH	–	CRP, 14.5 mg/dL; ALT, 154 U/L
Elevated ferritin	4. Ferritin > 500 ng/mL	Ferritin, 905 ng/mL
Abnormal TG or fibrinogen	5. TG > 265 mg/dL or fibrinogen < 150 mg/dL	TG, 358 mg/dL; fibrinogen, 500 mg/dL
High IL-6 or IL-10	6. Soluble IL-2 receptor > 2400 U/mL	–
–	7. Low or absent NK cell function	–
–	8. Haemophagocytosis in BM, liver, or lymph nodes	–
II. Organ dysfunction ≥ 2 organs (5)	(Organ dysfunctions as a principal feature of MAS)	II. Organ dysfunction: 4 organs involved
Cardiac (50%), shock (49%), mucocutaneous (74%), gastrointestinal (92%) hematologic (55%), or neurologic (15%)	Haemorrhagic, hepatic, and neurologic symptoms: frequent	Cardiac (troponin), shock (–), mucocutaneous (–), gastrointestinal (abdominal CT), hematologic (INR), neurologic (aseptic meningitis)
III. Infectious triggers	(Infection-associated hemophagocytic syndrome)	III. Infectious triggers
Laboratory evidence of COVID-19, confirmed by SARS-CoV-2-specific PCR, antigen, or antibodies tests	EBV, CMV, HHV-6, HIV-1, H1N1 influenza, *Mycoplasma, Staphylococcus, Salmonella, Leishmania,* or *Ehrlichia*	COVID-19 PCR positive 4 weeks prior

MIS-C: multisystem inflammatory syndrome in children; MAS: macrophage activation syndrome; CDC: Centres for Disease Control and Prevention; RCPCH: Royal College of Paediatrics and Child Health; HLH: haemophagocytic lymphohistiocytosis; CT: computed tomography; CRP: C-reactive protein; PCT: procalcitonin; AST: aspartate transaminase; ALT: alanine transaminase; LDH: lactate dehydrogenase; IL: interleukin; TG: triglycerides; –: absent or not available; NK: natural killer; BM: bone marrow; INR: international normalised ratio; COVID-19: coronavirus disease 2019; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; PCR: polymerase chain reaction; EBV: Epstein-Barr virus; CMV: cytomegalovirus; HHV: human herpes virus; HIV: human immunodeficiency virus.

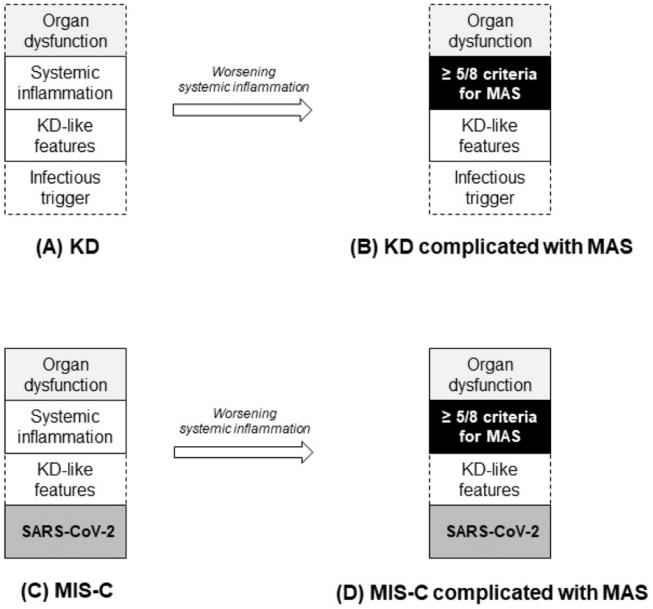

Fig. 1. Relationships between **(A)** KD and **(B)** KD complicated with MAS and between **(C)** MIS-C and **(D)** MIS-C complicated with MAS. Infectious triggers and organ dysfunction may be found in KD but are not included in the criteria for KD. Likewise, KD-like features are often found in MIS-C but are not essential for the diagnosis of MIS-C. If severe systemic inflammation (i.e., ≥5/8 criteria for MAS) is identified in patients with KD or MIS-C, they are diagnosed as 'KD complicated with MAS' or 'MIS-C complicated with MAS'.
KD: Kawasaki disease; MAS: macrophage activation syndrome; ≥5/8 criteria for MAS: 5 or more of 8 criteria for MAS; MIS-C: multisystem inflammatory syndrome in children; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2.

(Table I). This finding indicates that the two diseases share important pathophysiology, such as a cytokine storm (6, 12). Different cut-off points for variables may reflect the severity between MIS-C and MAS (4). In actual practice, development of MAS is a hallmark of severe MIS-C in terms of systemic inflammation and organ dysfunction (8, 12). A relatively high incidence of MAS and a MAS-like cytokine profile have been reported in patients with severe MIS-C (9, 12). MIS-C complicated with MAS may be more frequent than expected. Buda *et al*. (11) reported that approximately 20% (59/274) of MIS-C patients met the 2016 MAS classification criteria, which is much higher than the MAS incidence in sJIA (~13%), SLE (~5%), and KD (~2%) (4, 7). In conclusion, MAS may be under-recognised in various paediatric inflammatory diseases, including MIS-C. As shown in this case report, there may be severe, atypical cases of MIS-C that are complicated with MAS but do not have KD-like features.

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This study was approved by the Institutional Review Board of Bucheon St. Mary's Hospital, College of Medicine, The Catholic University of Korea (approval no.: HC23ZASI0082).

Competing interests: none declared.

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